

REMARKS

Applicants hereby affirm the election of Group II, claims 1-3 (part), drawn to processes using III, IV, or V. The election is made without waiver or prejudice to Applicants' right to pursue non-elected subject matter by way of one or more divisional applications.

The amendments have been made for the following reasons:

The Abstract has been replaced with a new Abstract on its own separate pages. The new Abstract, in response to the Examiner's comments on page 8 of the Office Action, employs formulas.

Claim 1 has been amended to state that the hydroxide trapping agent is a particular type of ester, as supported by the text bridging pages 10 and 11 of the specification.

Reference to formula (II) in claim 1 (and to formula (IIA) in claim 2) has been deleted as directed to non-elected subject matter (i.e., of Group I) due to the restriction requirement.

Claims 4-8 have been canceled as being drawn to non-elected subject matter classified in Group III.

Reference to "prodrugs" has been deleted from claim 1.

Substituents for 'Het' have been specified in claim 1, as supported at page 5, lines 6-9 and page 6, lines 5-6

"SOR¹⁸" has been changed to "S(O)R¹⁸" at page 62, line 28. This represents the correction of a typographical error.

Claims 1-3 were rejected as being drawn to an improper Markush Group. The Examiner stated that the rejection would be overcome by cancellation of the starting material choice (II). As such cancellation has been effected, it is respectfully requested that the rejection be withdrawn.

Claim 1 stands rejected under 35 USC 102(b) over Bunnage, US 6,251,904 B1 (Bunnage). The rejection is traversed on the basis that Bunnage does not disclose a hydroxide trapping agent, as required by Applicants. Nor does Bunnage specify the particular class of ester hydroxide trapping agents now required by Applicants' claims. The standard for anticipation is one of strict identity, meaning that for prior art to anticipate, it must contain all of the essential elements. Hybritech Inc.

v. Monoclonal Antibodies, Inc. 231 USPQ 81 (Fed Cir 1986). See In re Donohue, 226 USPQ 619 (Fed Cir 1985) where it was stated:

an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device.

Because Bunnage does not meet all of the limitations of claim 1, it cannot anticipate. Withdrawal of the rejection under §102(b) is accordingly respectfully requested.

It is noted the Examiner took the position that the scope of a hydroxide trapping agent is unknown and could include alcohols and ethers (as disclosed in Bunnage). Applicants contend that the skilled person would readily understand exactly what is meant by the term 'hydroxide trapping agent', i.e., an agent which would react with hydroxide thereby rendering it inactive in the reaction. It would quench the hydroxide, which could play no further part in the reaction, thereby reducing side-reactions and increasing yields (page 10 lines 1-3).

It would also be understood by the skilled person that alcohols and ethers would NOT act as hydroxide trapping agents. As the Examiner notes, there will be some degree of exchange, but the extent of this would be insignificant due to the differences in pKa, such that alcohols and ethers will NOT trap hydroxide.

In any event, Applicants have now amended their claims to specify the particular type of ester hydroxide trapping agent, and there can be no question that ethers and alcohols are not within the scope of Applicants' claims as hydroxide trapping agents.

The Examiner sought to support his contention (that alcohols may be hydroxide trapping agents) by citing the use of butanol in Applicants' claim 3. Butanol is not present as a hydroxide trapping agent. The trapping agent disclosed in claim 3 is n-butyl acetate. As disclosed in the description on page 10, line 28, esters are a preferred class of hydroxide trapping agents. In the case of claim 3, this relates to a preferred process for the preparation of the compound of formula IA, wherein QR3 = n-butoxy. The n-butyl acetate therefore reacts with hydroxide to produce unreactive acetate and n-butoxide, which is also the nucleophile used in the reaction and does not therefore result in side reactions and the creation of unwanted by-products.

Claim 1, and claims 1 and 3, stand provisionally rejected, respectively, under the judicially created doctrine of double patenting over claim 25 of copending US

Appln. No. 09/684228, and over claims 1-27 of 09/684853. It is believed that the Examiner's citation of "claim 25" in 09/684228 was likely a typo for "claim 22", and Applicants have assumed that the rejection intended "claim 22", rather than claim 25, in responding.

In respect of the rejection of claim 1 over claim 25 (22) of 09/684228, the process of the claim does not cover the use of a hydroxide trapping agent of any type and there is nothing in the application which would suggest the use of a hydroxide trapping agent or that improved yields can be achieved by their use. And, there is no suggestion of the particular type of ester trapping agent required by Applicants' claim 1 as now amended. Without such disclosure or suggestion in the claims of the double patenting reference, Applicants instantly claimed invention cannot be obvious.

In respect of the double patenting rejection of claim 1 over claims 1-27 of 09/684853, 09/684853 covers $R_4 = SO_2NR_3R_4$, which is not covered by the present application. Further, there is nothing in 09/684853 to suggest that the reaction would work for anything other than the $R_4 = SO_2NR_3R_4$, meaning that the present application is, therefore, unobvious. It is well accepted that for obviousness to lie, the reference(s) must supply a suggestion to do that which Applicants have invented, and must also provide a reasonable expectation of success. American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 USPQ 577, 582 (Fed. Cir. 1984). The Federal Circuit has explained the proper test:

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out **and would have a reasonable likelihood of success**, viewed in light of the prior art. **Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure** (emphasis added).

In re Dow Chemical Co., 5 USPQ.2d 1529, 1531 (Fed. Cir. 1988); Amgen, Inc. V. Chugai Pharmaceutical Co. Ltd. 18 USPQ.2d 1016. 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The double patenting reference provides no such expectation of success here since it concern a wholly different set of compounds.

In respect of the double patenting rejection of claim 3 over claims 1-27 of 09/684853, there is nothing in the claims of 09/684853 that suggests the specific combination of reagents claimed in claim 3, or that provides any other type of guidance which would render claim 3 obvious. Claim 3 is therefore unobvious over

the claims of 09/684853.

It is accordingly respectfully requested that the double patenting rejections be withdrawn.

Claims 1-3 stand rejected under 35 USC 112, second paragraph, as being indefinite. Prior to addressing the points raised by the Examiner, it would be useful to review the legal standard for definiteness. The standard for definiteness is whether the claims are clear as they stand and would be readily understandable to one skilled in the art. That is, if those skilled in the art would have no difficulty understanding the subject matter intended, that is all that the second paragraph of §112 requires. The Patent Act "requires only reasonable precision in delineating the bounds of the claimed invention." United States v. Teletronics, Inc., 8 USPQ2d 1217 (fed. Cir. 1988). Also,

The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification... If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more.

See Miles Laboratories Inc. v. Shannon Inc., 27 USPQ2d 1123 (Fed. Cir. 1993), at page 1126.

The Examiner advanced a number of grounds of indefiniteness, each being addressed by Applicants as follows:

Points 1, 2: The term "prodrug" has been deleted from claim 1.

Point 3: It is submitted that the phrase 'and/or terminated' adds clarity to what is claimed in that the substituent can be at the end of a chain. Applicants fail to see why this should be objected to. Those skilled in the art would have no problem understanding exactly what is intended, in keeping with the legal standard as reviewed above.

Point 4: Applicants have specified optional substituents from the definition of Het in the description on page 5, lines 6-9 and at page 6, lines 5-6.

Point 5: It is submitted that the Examiner's objection based on "what else is in the ring" is unfounded. It is clear what is meant by the definition, which is commonly used terminology. R14 and R15 together form a heterocyclic ring containing nitrogen. The definition of heterocyclic rings is disclosed (page 5, lines 19-31). It is therefore clear and unambiguous what is claimed, particularly in light of the

specification. There would be no problem with understanding on the part of the skilled art worker.

Point 6: The last choice on page 62 refers to -S(O)R18 and NOT -S-O-R18. Again this is commonly used terminology and is clear. Applicants have, however, corrected the missing parentheses in compliance with the Examiner's comments.

Point 7: Applicants believe the term "hydroxide trapping agent" is clear, as discussed previously (in connection with the §102 rejection over Bunnage), and that it is a standard term of art. Hydroxide = OH(-) and trapping agents trap. It is respectfully submitted that this terminology would be well understood in the art.

Points 8 and 12: Again, it is submitted that the term "auxiliary base" is standard chemical terminology. The answer to the Examiners question (regarding whether it is auxiliary to something else) is "yes". The Examiner appears to have answered his own question on how an auxiliary base differs from a regular base by his comments as set forth in point 12. Potassium carbonate is the auxiliary base. R3 is NOT C(O)OK. Potassium carbonate acts as an auxiliary base by reacting with the solvent n-butanol to form n-butoxide anion which is the base that acts to cyclise the ring (and that also acts as the nucleophile in the displacement of leaving group X).

Point 9: The parenthetical language objected to by the Examiner has been deleted.

Point 10: R³ is in fact defined. R³ is n-butoxy as defined in claim 2, page 67, lines 3-4.

Point 11: Applicants submit the language and usage are clear and unambiguous, and that the language employed is readily understood by those skilled in the art. Also, there clearly can not be a triple negative charge on an alkoxide.

Point 12: See point 8 above.

Point 13: A readily apparent typographical error (use of the word "and" where "from" should have been used after "(IA)") has been corrected so that the meaning of the wording referred to by the Examiner, in context, is clear.

In view of Applicants comments as presented above, it is respectfully submitted that the various points of rejection, listed as points 1-13, have been overcome and/or obviated, and it is respectfully requested that the various points of rejection be withdrawn.

On pages 7 and 8 of the Office Action, the Examiner made several additional rejections under 35 USC §112. Applicants respond to each as follows.

Claims 1-2 stand rejected as either not being enabled or as not being clearly described. The rejection, which appears to be a continuation of Point 11 previously made by the Examiner and discussed above, is based on Applicants use of OR^3 , which the Examiner contended is either problematic or inaccurate.

The rejection is traversed. The term is clear and it is respectfully submitted that the Examiner's contentions are misplaced. It would be clear to the skilled person what was meant by 'in the presence of (-)OR3', such terminology being standard in patents. The claim does not refer to 'adding an anion to the reaction'. All reagents which produce the anion in the reaction are covered. Preferred reagent include salts of the anion (page 12, lines 9-17) such as ZOR3. Thus it is Applicants' position that the claim language objected to would be readily understood by one "skilled" in the art, particularly in view of the specification, in light of which the claims are interpreted. United States v. Teletronics, Inc., supra.

Claim 3 stands rejected under 35 USC §112, although the basis for the rejection is not understood. The rejection appears to be grounded in Applicants' choice for R^3 , although point 11 (to which the Examiner refers) appears to be related to an entirely different issue. The rejection would more logically appear, in context, to relate to the Examiner's point 12, and this is what Applicants have assumed. If the examiner did intend to refer to his point 12, then Applicants have supplied the answer above, in the course of answering the Examiners points 8 and 12 - - the potassium carbonate is an auxiliary base, not R^3 .

Claim 1 stands rejected as being non-enabled, the Examiner having contended that the specification does not reasonably provide enablement for $\text{Q} = \text{NR}^5$ when III or IV is used. Applicants have now, by proviso, specified that Q is not NR^5 when a compound of formula (III) or (IV) is used in the claimed process. By this amendment, it is respectfully submitted that the rejection has been obviated, and withdrawal of same is respectfully requested.

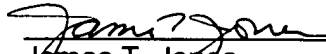
Claim 1 stands rejected under 35 USC §112 as being non-enabled. The Examiner appears to believe that the reaction would not work for certain specified values of R_4 due to their reactivity as leaving groups under the reaction conditions. Applicants point out that such groups would be stable under the reaction conditions

because the position on the pyridyl ring adjacent to the nitrogen (i.e., where the leaving group X is situated) is much more reactive (10-50 x) than the position 2 carbons away where R4 is situated. The only group which might cause problems in this respect is OC(O)R7 which Applicants have now deleted in order to expedite prosecution of the application.

In view of the foregoing comments and amendments, no outstanding issues are seen to be extant. This application is accordingly believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

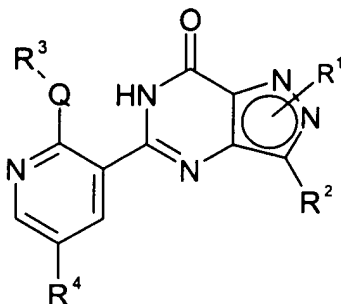
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VERSION MARKED UP TO SHOW CHANGES MADE

1. A process for the preparation of a compound of general formula (I):



I

or a pharmaceutically or veterinarily acceptable salt, ~~pro-drug~~,
polymorph and/or solvate thereof, wherein

Q represents O or NR³

R¹ represents H, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR⁶, OC(O)R⁷, C(O)R⁸, C(O)OR⁹, C(O)NR¹⁰R¹¹, NR¹²R¹³ and SO₂NR¹⁴R¹⁵)

R² represents H, halo, cyano, nitro, OR⁶, OC(O)R⁷, C(O)R⁸, C(O)OR⁹, C(O)NR¹⁰R¹¹, NR¹²R¹³, SO₂NR¹⁴R¹⁵, lower alkyl, Het, alkylHet, aryl or alkylaryl (which latter five groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR⁶, OC(O)R⁷, C(O)R⁸, C(O)OR⁹, C(O)NR¹⁰R¹¹, NR¹²R¹³ and SO₂NR¹⁴R¹⁵)

R³ represents H, lower alkyl, alkylHet or alkylaryl (which latter three groups are all optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR⁶, OC(O)R⁷, C(O)R⁸, C(O)OR⁹, C(O)NR¹⁰R¹¹, NR¹²R¹³ and SO₂NR¹⁴R¹⁵)

R⁴ represents H, halo, cyano, nitro, halo(loweralkyl), OR⁶, ~~OC(O)R⁷~~, C(O)R⁸, C(O)OR⁹, C(O)NR¹⁰R¹¹, NR¹²R¹³, NR¹⁶Y(O)R¹⁷, N[Y(O)R¹⁷]₂, S(O)R¹⁸, ~~SOR¹⁸~~, SO₂R¹⁹, C(O)AZ, lower alkyl, lower alkenyl, lower alkynyl, Het, alkylHet, aryl, alkylaryl (which latter seven groups are all optionally substituted

and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6 , $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

Y represents C or S(O)

A represents lower alkylene

Z represents OR^6 , halo, Het or aryl (which latter two groups are both optionally substituted with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6 , $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10}R^{11}$, $NR^{12}R^{13}$ and $SO_2NR^{14}R^{15}$)

R^{10} and R^{11} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from halo, cyano, nitro, lower alkyl, halo(loweralkyl), OR^6 , $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12}R^{13}$, $SO_2NR^{14}R^{15}$ and $NR^{20}S(O)_2R^{21}$ or Het or aryl optionally substituted with one or more of said latter thirteen groups) or one of R^{10} and R^{11} may be lower alkoxy, amino or Het, which latter two groups are both optionally substituted with lower alkyl

R^{10a} and R^{11a} independently represent R^{10} and R^{11} as defined above, except that they do not represent groups that include lower alkyl, Het or aryl, when these three groups are substituted and/or terminated (as appropriate) by one or more substituents that include one or more $C(O)NR^{10a}R^{11a}$ and/or $NR^{12}R^{13}$ groups

R^{12} and R^{13} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents selected from OR^6 , $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$), one of R^{12} or R^{13} may be C(O)-lower alkyl or C(O)Het (in which Het is optionally substituted with lower alkyl), or R^{12} and R^{13} together represent C_{3-7} alkylene (which alkylene group is optionally unsaturated, optionally substituted by one or more lower alkyl groups and/or optionally interrupted by O or NR^{26})

R^{14} and R^{15} independently represent H or lower alkyl or R^{14} and R^{15} , together with the nitrogen atom to which they are bound, form a heterocyclic ring

R^{16} and R^{17} independently represent H or lower alkyl (which latter group is optionally substituted and/or terminated with one or more substituents

selected from OR^6 , $C(O)OR^9$, $C(O)NR^{22}R^{23}$ and $NR^{24}R^{25}$) or one of R^{16} and R^{17} may be Het or aryl, which latter two groups are both optionally substituted with lower alkyl

R^5 , R^6 , R^7 , R^8 , R^9 , R^{18} , R^{19} , R^{20} , R^{22} , R^{23} , R^{24} and R^{25} independently represent H or lower alkyl

R^{18} and R^{19} independently represent lower alkyl

R^{21} represents lower alkyl or aryl

R^{26} represents H, lower alkyl, aryl, $C(O)R^{27}$ or $S(O)_2R^{28}$

R^{27} represents H, lower alkyl or aryl

R^{28} represents lower alkyl or aryl

Het represents ~~a~~ an optionally substituted four- to twelve-membered heterocyclic group, optionally substituted by one or more substituents selected from halo, cyano, nitro, oxo, lower alkyl (which alkyl group may itself be optionally substituted by halo), OR^6 , $OC(O)R^7$, $C(O)R^8$, $C(O)OR^9$, $C(O)NR^{10a}R^{11a}$, $NR^{12a}R^{13a}$ and $SO_2NR^{14}R^{15}$, which group contains one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof

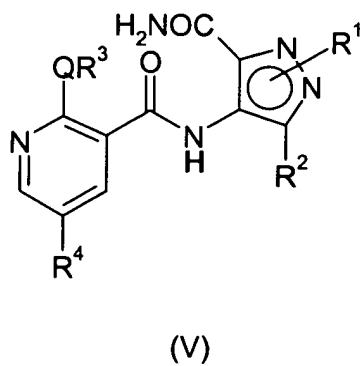
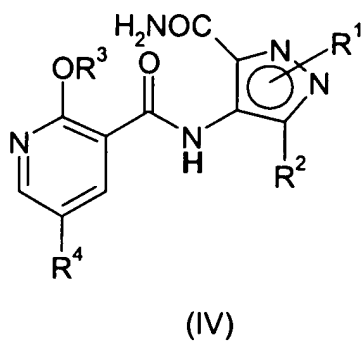
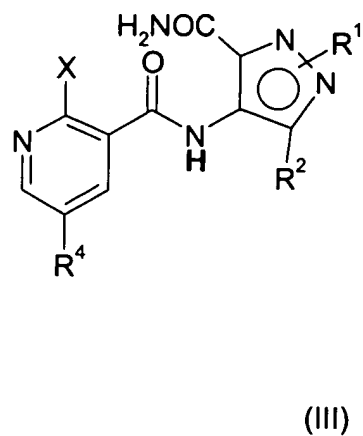
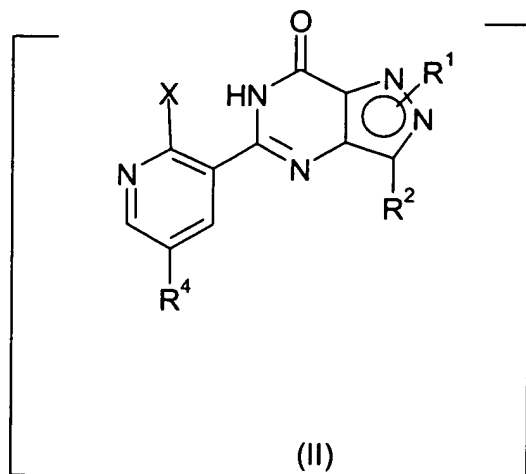
said process comprising reacting a compound of formula (II), (III), (IV) or (V) in the presence of $^-OR^3$ and a hydroxide trapping agent which is an ester of the formula

$TOC(O)W$

wherein OT is OR^3 or OT is the residue of a bulky alcohol or a non-nucleophilic alcohol or TOH is an alcohol which can be azeotropically removed during the reaction;

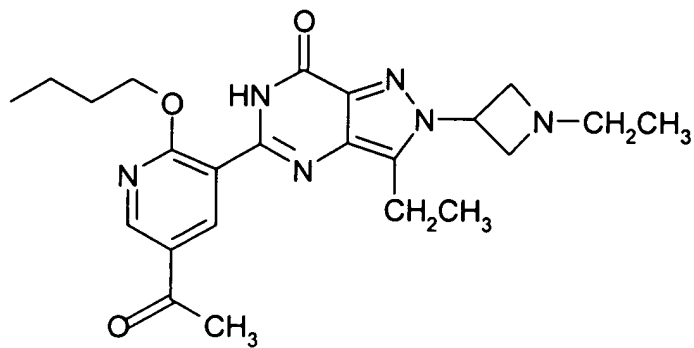
and $C(O)W$ is the residue of a carboxylic acid;

or, alternatively, in the case of compounds of formulae (IV) or (V) reacting in the presence of an auxiliary base and a hydroxide trapping agent (~~i.e. $^-OR^3$ is substituted by the auxiliary base~~)



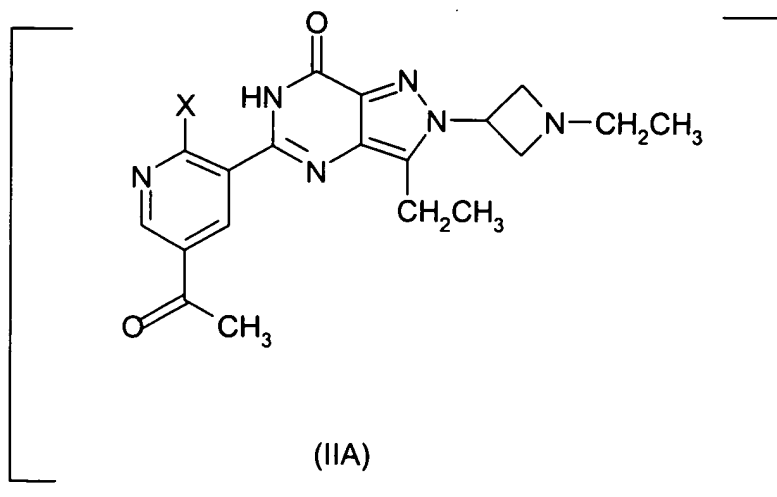
wherein X is a leaving group and Q and R¹ to R⁴ are as defined above,
provided that in said process, Q is not NR⁵ when a compound of
 formula (III) or (IV) is used therein.

2. A process for the preparation of a compound of formula (IA):

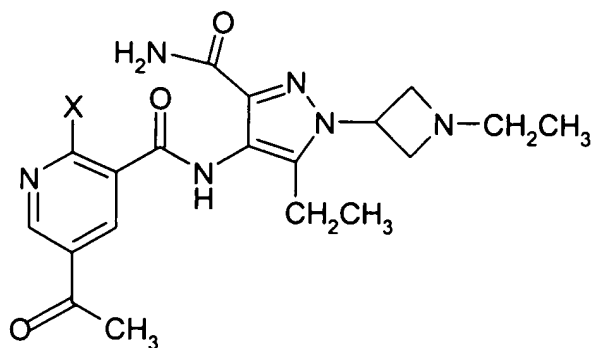


(IA)

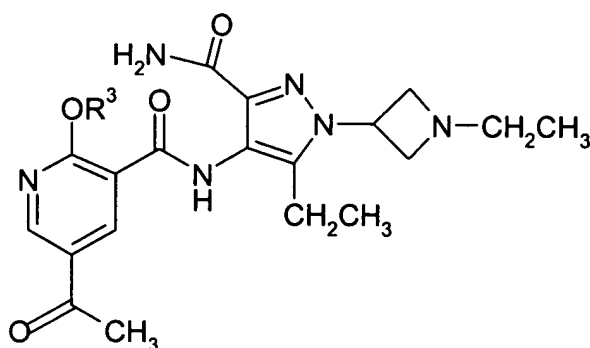
said process comprising reacting a compound of formula (IIA), (IIIA) or (IVA) respectively



(IIA)



(IIIA)



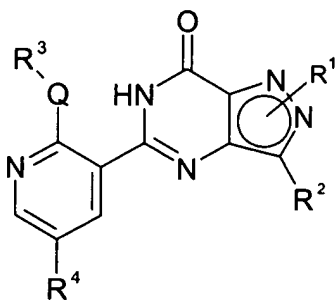
(IVA)

in the presence of OR^3 and a hydroxide trapping agent, or alternatively in the case of compounds of formula (IVA) reacting in the presence of a hydroxide trapping agent and an auxiliary base, wherein OR^3 in the case of formation of compound (IA) from ~~and~~ (IVA) is $\text{CH}_3(\text{CH}_2)_3\text{O}^-$ and wherein X in formulae (IIA) ~~and~~ (IIIA) is a leaving group.



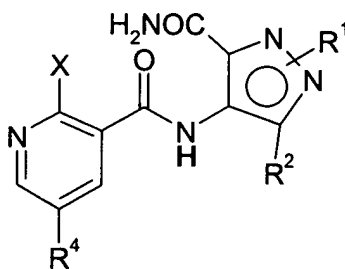
Abstract

A process is provided for the preparation of compounds of formula (I) herein

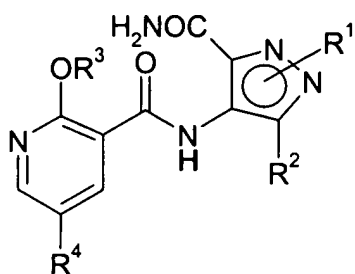


I

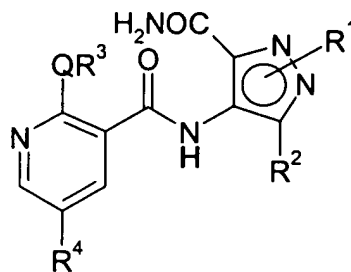
comprising reacting a compound of formula (III), (IV) or (V)



(III)



(IV)



(V)

wherein the variables are as defined in the specification. The reaction is conducted in the presence of OR^3 and a hydroxide trapping agent or in the case of compounds of formula (IV) reacting in the presence of an auxiliary base and a hydroxide trapping agent.